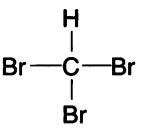
Bromoform

CAS #75-25-2
Swiss CD-1 mice, at 0.0, 50, 100, and 200 mg/kg by gavage
Robert Chapin, NTP/NIEHS Project Officer
Dushyant Gulati, Esther Hope, Robin Mounce, Susan Russell, and K.B. Poonacha, Environmental Research and Testing
Started 12/30/86; Completed 2/15/89
NTIS #PB89169254/AS



Bromoform, which is present in drinking water supplies at low microgram to nanogram levels, was tested for its effects on reproduction and fertility in Swiss CD-1 mice, following the RACB protocol. Data on body weights, clinical signs, and food and water consumption from a 2-week dose-range-finding study (Task 1) were used to set exposure levels for the Task 2 continuous cohabitation phase at 50, 100, and 200 mg/kg/day by gavage. With a single exception, dosing formulations were 90 to 110% of nominal concentrations.

During Task 2 six animals died from parturition complications, infection, and skin wounds inflicted by the partner, which occurred in all dose groups and were not related to treatment. Water consumption was increased for high dose animals by approximately 16%. Starting with the first litter, postpartum dam weights were lower in the high dose group, compared to controls, by 3 to 8%. Other dose levels, and male body weights, were unaffected.

In Task 2, there were no treatment-related changes in reproductive end points: number of litters per pair, live pups per litter, viability, and pup body weights were all unaffected by these levels of bromoform exposure. The average study day for litter delivery was not affected by treatment. In the absence of a reproductive effect to investigate, no crossover tests were performed.

The last litters from all dose groups were nursed by their dams until weaning. Bromoform exposure increased neonatal mortality by 15 to 20% at the high dose only in the first 4 days postnatally. Pup body weight was occasionally significantly reduced in high dose pups prior to weaning.

At weaning, the F_0 mice were killed and discarded without necropsy. Following the protocol of a "negative" study, at weaning the pups from the low and middle dose groups were killed and discarded, and the pups from the control and high dose groups were reared and dosed through the mating period (at 74 ± 10 days of age) until necropsy.

During the F_1 mating trial, there were no differences between the two groups with respect to mating or fertility index. The number, viability, and weight of pups were not affected by bromoform exposure.

After the F_2 pups were delivered and evaluated, the F_1 adults were killed and necropsied. While female body weights were unaffected by exposure to 200 mg/kg/day bromoform, relative liver weight was increased by 8%, and relative kidney weight was decreased by 6%. Vaginal cyclicity was not examined in these mice. In males, body weights of the exposed mice were reduced by 6%, while weight-adjusted liver weights were increased by 6% and adjusted kidney weights were reduced by 6%. There were no changes in other organ weights or in epididymal sperm parameters.

Microscopically, varying degrees of hepatocellular degeneration was seen in all treated male and female mice. No treatment-related alterations were noted in kidney, thryoid, lung, or sex organs.

In summary, bromoform caused a slight increase in postnatal mortality, but no changes in other reproductive indices, at doses that caused significant hepatotoxicity.

Summary: NTP Reproductive Assessment by Continuous Breeding Study.

NTIS#: **89169254/AS**
Chemical: **Bromoform**
CAS#: **75-25-2**
Mode of exposure: **Gavage**
Species/strain: **Swiss CD-1 mice**

F_0 generation — Dose concentration →	50 mg/kg	100 mg/kg	200 mg/kg
General toxicity	Male, female	Male, female	Male, female
Body weight	—, —	—, —	—, ↓
Kidney weight[a]	•	•	•
Liver weight[a]	•	•	•
Mortality	—, —	—, —	—, —
Feed consumption	•	•	•
Water consumption	—, —	—, —	↑, ↑
Clinical signs	—, —	—, —	—, —
Reproductive toxicity			
x̄ litters/pair	—	—	—
# live pups/litter; pup wt./litter	—, —	—, —	—, —
Cumulative days to litter	—	—	—
Absolute testis, epididymis weight[a]	•	•	•
Sex accessory gland weight[a] (prostate, seminal vesicle)	•	•	•
Epidid. sperm parameters (#, motility, morphology)	•	•	•
Estrous cycle length	•	•	•

Determination of affected sex (crossover)	Male	Female	Both
Dose level	•	•	•

F_1 generation — Dose concentration →	•	•	200 mg/kg
General toxicity	Male, female	Male, female	Male, female
Pup growth to weaning	—, —	—, —	—, —
Mortality	—, —	—, —	↑, ↑
Adult body weight	•	•	↓, —
Kidney weight[a]	•	•	↓, ↓
Liver weight[a]	•	•	↑, ↑
Feed consumption	•	•	•
Water consumption	•	•	—, —
Clinical signs	—, —	—, —	—, —
Reproductive toxicity			
Fertility index	•	•	—
# live pups/litter; pup wt./litter	•	•	—, —
Absolute testis, epididymis weight[a]	•	•	—, —
Sex accessory gland weight[a] (prostate, seminal vesicle)	•	•	—, —
Epidid. sperm parameters (#, motility, morphology)	•	•	—, —, —
Estrous cycle length	•	•	•

Summary information	
Affected sex?	Unclear
Study confounders:	None
NOAEL reproductive toxicity:	200 mg/kg
NOAEL general toxicity:	<200 mg/kg
F_1 more sensitive than F_0?	Unclear
Postnatal toxicity:	Yes

Legend: —, no change; •, no observation; ↑ or ↓, statistically significant change ($p<0.05$); —, —, no change in males or females. [a]Adjusted for body weight.